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| APPLICATION NO.   | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.        | CONFIRMATION NO. |
|---|-------------|----------------------|----------------------------|------------------|
| 10/523,412  | 11/07/2005  | Jan Geert Sterk      | 26565U                     | 6295             |
| 34375   | 7590        | 10/24/2006           |                            |                  |
| NATH & ASSOCIATES PLLC<br>112 South West Street<br>Alexandria, VA 22314 |             |                      |                            |                  |
|   |             |                      | EXAMINER<br>HABTE, KAHSA Y |                  |
|   |             |                      | ART UNIT<br>1624           | PAPER NUMBER     |

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/523,412

**Applicant(s)**

STERK, JAN GEERT

**Examiner**

Kahsay Habte

**Art Unit**

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-12, 14 and 17-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 11-12 is/are allowed.
- 6) ☒ Claim(s) 1-10, 14 and 17-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>4/28/2005</u> . | 6) <input type="checkbox"/> Other: ____.  |

### **DETAILED ACTION**

1. Claims 1-12, 14 and 17-24 are pending in this application.

#### ***Information Disclosure Statement***

2. Applicant's Information Disclosure Statement, filed on 04/28/2005 has been acknowledged. Please refer to Applicant's copies of the 1449 submitted herewith.

#### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is recited in claim 17, a method for treating a disease treatable by the administration of a PDE4 inhibitor, but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered.

Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

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or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled. There are myriad diseases at page 14 that are mediated by PDE4. There is no complete list of the diseases. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents having antiviral activity, useful to treat viral infections in general. Test procedures and assays are provided in the specification at page 18 only for 1 compound and it is concluded that the representative compound 1 demonstrated positive inhibitory activity with  $-\log IC_{50}$  of 10.66 mol/L, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims, some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The claims are drawn to the treatment of various types of diseases disclosed at page 18 of the specification, however, there is no common mechanism by which all conditions can be treated with a single pharmaceutical drug due the nature of these diseases.

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Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

It is recommended that applicants delete this claim to overcome this rejection.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 14 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula I, pharmaceutically acceptable salts thereof, does not reasonably provide enablement for hydrates and solvates of the compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making the determination of whether or not a claimed invention is supported by a given disclosure to sufficient to enable a person of ordinary skill in the art to which

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it pertains, to make and/or use the invention, given said disclosure, the Office relies upon factors promulgated in the decision rendered in *In re Wands*:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 858 F.2d 731, 737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Each factor will be addressed in the following:

- (A) Insofar as the solvate embodiment of claims 1-10, 14 and 17-24 are concerned, those claims read on hydrates and solvates of compounds according to formula I. The scope of these solvates recited in the claims includes solvates of a compound according to formula (I), with *any* solvent. The definition of a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a "crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or non-stoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug." The number of specific solvates, embraced by instant claim 1, and the claims that depend from that claim, is essentially incalculable.
- (B) The nature of the invention is that of a chemical compound's specific solvate and hydrate forms.
- (C), (D), (E) Hydrates and solvates, at the time the invention was made, were known and could be identified, but not understood to such an extent that the directed

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preparation thereof was routine or simple. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the predictability thereof.

Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), wherein all of the factors relevant to each individual compound's ability to crystallize and form solvates are studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

It is unknown that the full scope of solvates of compounds of formula (I) is even possible (see Gavezzotti, page 309, point #1).

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(F) Aside from a mention that the invention includes solvates of formula (I) compounds (at page 1, line 18) no guidance relevant to preparation of solvates is provided in the disclosure. In the specification, it is disclosed that "According to expert's knowledge the compounds may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefor all solvates and in particular all hydrates of the compounds of formula 1 as well as all solvates and in particular all hydrates of the salts of the compounds of formula 1".

(G) There is nothing in the disclosure that demonstrates the preparation of a solvate or a hydrate.

(H) Each compound of formula I, of which there are thousands upon thousands, as a solvate with every solvent within the scope of "solvate" generally, of which there are also thousands upon thousands, represents the efforts of many over a period of years. Those efforts are likely never to be completed, due to the sheer number of possible compound/solvent combinations. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al. for preparation of every one of the claimed solvates would clearly be undue. Applicants' right to exclude others from making all solvates of compounds according to formula (I) is unwarranted in light of the lack of any direction as to how one of ordinary skill would do so.

It would be undue experimentation for a chemist to determine which compounds according to formula I will not form hydrates or solvates and which of them will, and how to make and identify those hydrates or solvates.

It is recommended that applicants amend the claim to its original claim language i.e. "and the salts of these compounds".

***Allowable Subject Matter***

5. Claims 11-12 are allowed.

***Conclusion***

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte whose telephone number is (571)-272-0667. The examiner can normally be reached on M-F (9.00- 5:30).

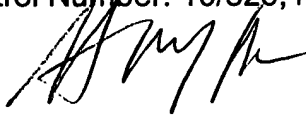
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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A handwritten signature in black ink, appearing to read 'Kahsay Habte', is written over the text 'Art Unit: 1624'.

Kahsay Habte  
Primary Examiner  
Art Unit 1624

KH  
October 18, 2006